FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, CAPLUS' ENTERED AT 12:26:54 ON 27 JAN 2003

L1 4986 S ANAPHYLATOXIN
L2 1040 S L1 (A) C3A
L3 88 S L2 (A) RECEPTOR
L4 37 DUP REM L3 (51 DUPLICATES REMOVED)
L5 16 S L4 AND MOUSE

FILE 'STNGUIDE' ENTERED AT 12:33:22 ON 27 JAN 2003

FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, CAPLUS' ENTERED AT 12:35:16 ON 27 JAN 2003

L6 209 S L1 (A) C5A (A) RECEPTOR
L7 26 S L6 AND (KNOCKOUT OR KO OR (KNOCK (A) OUT) OR MUTAT? OR MUTAN
L8 12 DUP REM L7 (14 DUPLICATES REMOVED)

L Number	Hits	Search Text	DB	Time stamp
1	8	anaphylatoxin adj c3a adj receptor	USPAT; US-PGPUB; DERWENT	2003/01/27 12:57

AN 2001254000 MEDLINE
DN 21240702 PubMed ID: 11342658
TI Identification of a selective nonpeptide antagonist of the **anaphylatoxin C3a receptor** that demonstrates antiinflammatory activity in animal models.
AU Ames R S; Lee D; Foley J J; Jurewicz A J; Tornetta M A; Bautsch W; Settmacher B; Klos A; Erhard K F; Cousins R D; Sulpizio A C; Hieble J P; McCafferty G; Ward K W; Adams J L; Bondinell W E; Underwood D C; Osborn R R; Badger A M; Sarau H M
CS Department of Molecular Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406-0939, USA.. bob_ames-1@sbphrd.com
SO JOURNAL OF IMMUNOLOGY, (2001 May 15) 166 (10) 6341-8.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809
AB The anaphylatoxin C3a is a potent chemotactic peptide and inflammatory mediator released during complement activation which binds to and activates a G-protein-coupled receptor. Molecular cloning of the C3aR has facilitated studies to identify nonpeptide antagonists of the C3aR. A chemical lead that selectively inhibited the C3aR in a high throughput screen was identified and chemically optimized. The resulting antagonist, N(2)-[(2,2-diphenylethoxy)acetyl]-L-arginine (SB 290157), functioned as a competitive antagonist of (125)I-C3a radioligand binding to rat basophilic leukemia (RBL)-2H3 cells expressing the human C3aR (RBL-C3aR), with an IC(50) of 200 nM. SB 290157 was a functional antagonist, blocking C3a-induced C3aR internalization in a concentration-dependent manner and C3a-induced Ca(2+) mobilization in RBL-C3aR cells and human neutrophils with IC(50)s of 27.7 and 28 nM, respectively. SB 290157 was selective for the C3aR in that it did not antagonize the C5aR or six other chemotactic G protein-coupled receptors. Functional antagonism was not solely limited to the human C3aR; SB 290157 also inhibited C3a-induced Ca(2+) mobilization of RBL-2H3 cells expressing the **mouse** and guinea pig C3aRS: It potently inhibited C3a-mediated ATP release from guinea pig platelets and inhibited C3a-induced potentiation of the contractile response to field stimulation of perfused rat caudal artery. Furthermore, in animal models, SB 290157, inhibited neutrophil recruitment in a guinea pig LPS-induced airway neutrophilia model and decreased paw edema in a rat adjuvant-induced arthritis model. This selective antagonist may be useful to define the physiological and pathophysiological roles of the C3aR.

6 MEDLINE
AN 2002676320 MEDLINE
DN 22309149 PubMed ID: 12421977
TI Absence of the complement **anaphylatoxin C3a receptor** suppresses Th2 effector functions in a murine model of pulmonary allergy.
AU Drouin Scott M; Corry David B; Hollman Travis J; Kildsgaard Jens; Wetsel Rick A
CS Institute of Molecular Medicine for the Prevention of Human Diseases, University of Texas-Houston Medical School, 2121 West Holcombe Boulevard, Houston, TX 77030, USA.
NC AI 10223 (NIAID)
AI 25011 (NIAID)
SO JOURNAL OF IMMUNOLOGY, (2002 Nov 15) 169 (10) 5926-33.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200301
ED Entered STN: 20021120
Last Updated on STN: 20030115
Entered Medline: 20030114
AB Asthma is a chronic inflammatory disease of the lung resulting in airway obstruction. The airway inflammation of asthma is strongly linked to Th2 lymphocytes and their cytokines, particularly IL-4, IL-5, and IL-13, which regulate airway hyperresponsiveness, eosinophil activation, mucus production, and IgE secretion. Historically, complement was not thought to contribute to the pathogenesis of asthma. However, our previous reports have demonstrated that complement contributes to bronchial hyperreactivity, recruitment of airway eosinophils, IL-4 production, and IgE responses in a **mouse** model of pulmonary allergy. To define the complement activation fragments that mediate these effects, we assessed the role of the complement anaphylatoxin C3a in a **mouse** model of pulmonary allergy by challenging C3aR-deficient **mice** intranasally with a mixed Ag preparation of Aspergillus fumigatus cell culture filtrate and OVA. Analysis by plethysmography after challenge revealed an attenuation in airway hyperresponsiveness in C3aR-deficient **mice** relative to wild-type **mice**. C3aR-deficient **mice** also had an 88% decrease in airway eosinophils and a 59% reduction in lung IL-4-producing cells. Consistent with the reduced numbers of IL-4-producing cells, C3aR-deficient **mice** had diminished bronchoalveolar lavage levels of the Th2 cytokines, IL-5 and IL-13. C3aR knockout **mice** also exhibited decreases in IgE titers as well as reduced mucus production. Collectively, these data highlight the importance of complement activation, the C3a anaphylatoxin, and its receptor during Th2 development in this experimental model and implicate these molecules as possible therapeutic targets in diseases such as asthma.

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AN 2002:343989 BIOSIS

DN PREV200200343989

TI Absence of the complement **anaphylatoxin C3a receptor** suppresses Th2 effector functions in a murine model of asthma.

AU Drouin, Scott M. (1); Corry, David B.; Kildsgaard, Jens (1); Hollmann, Travis J. (1); Wetsel, Rick A. (1)

CS (1) University of Texas-Houston, 2121 W. Holcombe Blvd., Suite 907, Houston, TX, 77030 USA

SO FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A682. http://www.fasebj.org/. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638.

DT Conference

LA English

AB Our previous report demonstrated that complement contributes to bronchial hyperreactivity, airway eosinophilia, IL-4 production, and IgE responses in a **mouse** model of asthma (J. Immunol., 2001, 167:4141-45). To elucidate the mechanisms that mediate these effects, we assessed the role of the complement anaphylatoxin C3a in a **mouse** model of asthma by challenging C3a receptor (C3aR)-deficient **mice** intranasally with Aspergillus fumigatus. Analysis by plethysmography after challenge revealed a 45% decrease in bronchial hyperreactivity in C3aR-deficient relative to wild-type **mice**. C3aR-deficient **mice** also had an 88% and 59% reduction in airway eosinophils and lung IL-4-producing cells, respectively. Consistent with the reduced numbers of IL-4-producing cells, C3aR-deficient **mice** had diminished BAL levels of the Th2 cytokines, IL-5 and IL-13, and a 39% decrease in serum IgE levels. These data highlight the importance of complement activation in airway inflammation, Th2 production of IL-4, and IgE responses during asthma. Moreover, these data support that much of the complement-mediated effects observed in this asthma model are due to the C3a anaphylatoxin and its receptor.

AN 97419192 MEDLINE
DN 97419192 PubMed ID: 9271590
TI Impaired inflammatory responses in the reverse arthus reaction through genetic deletion of the C5a receptor.
AU Hopken U E; Lu B; Gerard N P; Gerard C
CS Ina Sue Perlmutter Cystic Fibrosis Laboratory, Children's Hospital, Department of Medicine, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.
NC HL-36162 (NHLBI)
HL-51366 (NHLBI)
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Aug 29) 186 (5) 749-56.
Journal code: 2985109R. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971013
Last Updated on STN: 19980206
Entered Medline: 19971002
AB We recently demonstrated that gene-targeted disruption of the **C5a anaphylatoxin receptor** prevented lung injury in immune complex-mediated inflammation. In this study, we compare the effect of C5aR deficiency in immune complex-induced inflammation in the peritoneal cavity and skin with the results derived from our immune complex alveolitis model. C5aR- deficient mice exhibit decreased migration of neutrophils and decreased levels of TNF-alpha and interleukin 6 in the peritoneal reverse passive Arthus reaction compared to their wild-type littermates. In the reverse passive Arthus reaction in the skin the C5aR was also required for the full expression of neutrophil influx and edema formation; C5aR-deficient mice showed reduced neutrophil migration and microvascular permeability changes. In contrast to our studies in immune complex-induced lung inflammation, C5aR deficiency does not completely prevent injury in the peritoneal cavity and skin. These data indicate a dominant role for the C5aR and its ligand in the reverse passive Arthus reaction in the lung and a synergistic role together with other inflammatory mediators in immune complex-mediated peritonitis and skin injury.

Neurogenic Amplification of Immune Complex Inflammation

Carmen R. Bozic, * **Bao Lu,** * **Uta E. Höpken, Craig Gerard, Norma P. Gerard** †

The formation of intrapulmonary immune complexes in mice generates a vigorous inflammatory response characterized by microvascular permeability and polymorphonuclear neutrophil influx. Gene-targeted disruption of the substance P receptor (NK-1R) protected the lung from immune complex injury, as did disruption of the C5a anaphylatoxin receptor. Immunoreactive substance P was measurable in fluids lining the lung at time points before neutrophil influx and may thus be involved in an early step in the inflammatory response to immune complexes in the lung.

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Immune complexes underlie the inflammatory response seen in a variety of rheumatologic illnesses, including arthritis, vasculitides, and systemic lupus erythematosus (1). Antigen-antibody aggregates may be deposited locally and incite edema through enhanced microvascular permeability to plasma proteins as well as elicit exudates of acute inflammatory leukocytes typified by the polymorphonuclear neutrophil (PMN). The mechanisms of injury induced by the immune complex are modeled in experimental animals by the Arthus reaction, in which specific antibody and antigen are passively introduced across a vascular barrier (2). Studies on rabbit skin and in mice deficient in complement component C5 implicated complement proteins as crucial participants in the inflammatory response (3), a role that has been reinvestigated through the use of mast cell and Fc receptor-deficient mice (4). We now use strains of mice deficient in the receptors for substance P (NK-1R) and the complement anaphylatoxin C5a (C5aR) to define a mechanism for immune complex-mediated acute lung injury.

Mice deficient in NK-1R and C5aR (5) were generated by gene targeting. The NK-1R was cloned as a genomic copy from 129 Sv mice (Fig. 1A). Exon 1 was partially deleted, including the initiating methionine codon, and replaced with a cassette encoding *lacZ* and neomycin resistance. We used J1